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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/635,908	08/07/2003	Reinier Lh Bolhuis	2923-552	7844

6449 7590 12/24/2008

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EXAMINER	
DUFFY, BRADLEY	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
12/24/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

Office Action Summary	Application No.	Applicant(s)	
	10/635,908	BOLHUIS ET AL.	
	Examiner	Art Unit	
	BRADLEY DUFFY	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 October 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/29/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to comply*.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 4, 2008, has been entered.

2. The two declarations under 37 C.F.R. § 1.132 by Arko Gorter filed August 4, 2008, are acknowledged and have been entered.

3. The declaration under 37 C.F.R. § 1.132 by Gerd Ritter filed August 4, 2008, is acknowledged and has been entered.

4. Claims 1-11 are pending in the application and currently under prosecution.

Information Disclosure Statement

5. The references cited in the information disclosure statement filed August 29, 2008, have been considered. Notably, while considered, document 1 was crossed out because it does not properly identify the document as a published document and therefore does not conform to the information disclosure statement requirements. (See MPEP 609). Furthermore, document 2 has already been made of record in the Office action mailed 6/20/2006, and has been crossed out for this reason.

Priority

6. Applicant's claim under 35 USC §§ 119 and/or 120 for benefit of the earlier filing date of PCT/EP02/01283, filed February 7, 2002, US provisional application,

60/327,008, filed October 5, 2001, and US provisional application, 60/266,853, filed February 7, 2001, is acknowledged.

However, claims 1-11 do not properly benefit under 35 U.S.C. §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under 35 USC §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Furthermore, claims 1-11 do not properly benefit by the earlier filings because the prior applications do not contain written support for the claims for the reasons set forth in the below rejection of the instant claims as containing NEW MATTER.

Finally, the instant application does not benefit by US provisional application, 60/327,008, filed October 5, 2001, because this application does not share an inventor in common with the instant application. See 35 U.S.C. 120.

Accordingly, the effective filing date of the claims is deemed the filing date of the instant application, namely August 7, 2003.

Response to the Declarations under 37 C.F.R. § 1.132

7. The merit of the declarations under 37 C.F.R. § 1.132 filed December 14, 2007, have been carefully considered but are deemed insufficient to overcome the rejection of claims 1-11 under 35 U.S.C. 103, as set forth in the last Office action, for the following reasons:

In this case, the supplied declarations have been presented to evidence that neither the hybridoma producing the G250 monoclonal antibody, nor the G250 monoclonal antibody, which comprises the instantly recited amino acid sequences of

SEQ ID NO:24, 25, 25, 27, 28 and 29, was publicly available because the G250 antibody was only supplied to Drs. Gorter and Ritter under confidentiality agreement; but neither person is an inventor, so it is apparent that the antibody was made available to members of the public other than the inventors or persons under their direct supervision.

In further response, and after careful and complete consideration and further search, it is apparent that the G250 antibody was also made available to several others, none of whom are inventors or persons under their direct supervision, including, for example, the inventors or authors of the following publications: Lindholm (WO 200102431 A1, January 2001), Choudhary et al (Int. J. Can, 82:1562-1568, 1999), Danen (Exp Cell Res., 238:188-196, 1998), Lal et al (JNCI 93(17):1337-1343, 2001), Tso et al (Can Res., 61:7925-7933, 2001) and Shinkai (Jpn. J. Can Res, 92:1138-1145, 2001). Notably, as set forth in below 35 USC 102(b) rejection, Lindholm teaches the heavy and light chain sequences of a G250 antibody which comprises the instantly recited amino acid sequences. Accordingly, it is submitted that the G250 antibody was publicly available before the effective filing date of the instant claims.

Thus, although the merit of the declarations under 37 C.F.R. § 1.132 have been carefully and fully considered, it is for these reasons that they are deemed insufficient to overcome the rejection of claims 1-11 under 35 U.S.C. 103.

Grounds of Objection

8. The amendment filed December 20, 2006, is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: identifying H3 in Figure 1 as the amino acid sequence SGYFSMDY, i.e., SEQ ID NO:26.

Notably, as originally filed, Figure 1 identifies H3 with the amino acid sequence HRSGYFSMDY (see Figure 1).

Accordingly, it is submitted that amending the specification to recite that H3 is the amino acid sequence SGYFSMDY introduces new matter into the disclosure.

Otherwise this issue might be resolved if Applicant were to specifically point to other disclosures in the specification, including the claims, as originally filed, which are believed to support adding the above disclosure.

If this issue is not otherwise appropriately remedied, Applicant is required to cancel the new matter in the reply to this Office Action.

Drawings

9. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the brief description of the drawings: Figure 1, Figure 2, Figure 3A, Figure 3B, Figure 4, Figure 5 and Figure 6. In this case, the specification lacks a brief description of the drawings entirely. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

10. The drawings set forth as Figure 1, Figure 2, Figure 3A, Figure 3B, Figure 5 and Figure 6 are objected to because they depict amino acid and/or polynucleotide sequences, which are not identified by sequence identification numbers, either in the figure or in the brief description of drawings. Notably, the specification currently does not contain a brief description of the figures section; yet these sequences appear to be in the current sequence listing.

Applicant must provide appropriate amendments to the specification or drawings inserting the required sequence identifiers. Sequence identifiers for sequences

appearing in the drawings may appear in the drawings or in the brief description of the drawings.

Appropriate action correcting this deficiency is required. If any of the sequences disclosed are not in the current sequence listing, Applicant must submit paper and computer-readable copies of a substitute sequence listing, together with an amendment directing its entry into the specification and a statement that the content of both copies are the same and, where applicable, include no new matter.

Sequences appearing in the specification and/or drawings must be identified by a sequence identifier in accordance with 37 C.F.R. 1.821(d); sequence identifiers for sequences appearing in the drawings may appear in the drawings or in the brief description of the drawings.

A replacement drawing sheet, including the correction, is required, if the drawings are objected to. See 37 CFR 1.121(d). However, this ground of objection would be withdrawn, so that a replacement drawing would be not be required, if Applicant were to amend the specification to include a brief description of the figures section as required by 37 CFR 1.77, wherein the description indicates which SED ID NO: identifies the disclosed sequences, respectively, provided that the amino acid sequences presented in the figures are the same as the sequences given in the respective SEQ ID NO.

Appropriate correction is required.

Specification

11. The disclosure is objected to because of the following informalities:

(a) The specification is objected to because it fails to comply with the requirement set forth under 37 C.F.R. §§ 1.74 and 1.77. In this case, the specification lacks a “Brief Description of Drawings” section in accordance with the requirement of § 1.77, which describes the drawings in accordance with § 1.74. See M.P.E.P. § 608.01(a) and (f).

(b) The specification contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). Sequences appearing in the specification and/or drawings must be identified by sequence identifier in accordance with 37 C.F.R. 1.821(d). According to 37 CFR § 1.821(a), an unbranched sequence of four or more specifically identified amino acids or an unbranched sequence of ten or more nucleotides must be identified by sequence identification numbers. See MPEP § 2422.01.

In this instance, the sequences depicted in Figure 1, Figure 2, Figure 3A, Figure 3B, Figure 5 and Figure 6 are not identified by sequence identification numbers, either in the figure or in a section labeled "Brief Description of Drawings". Applicant must provide appropriate amendments to the specification or drawings inserting the required sequence identifiers. Sequence identifiers for sequences appearing in the drawings may appear in the drawings or in the brief description of the drawings.

As noted in the attached Notice to Comply, appropriate action correcting this deficiency is required. If necessary to correct the deficiency, Applicant must submit paper and computer-readable copies of a substitute sequence listing, together with an amendment directing its entry into the specification and a statement that the content of both copies are the same and, where applicable, include no new matter.

(c) The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior

art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. The rejection of claims 1-11 under 35 U.S.C. 103(a) as being unpatentable over Oosterwijk et al (a) (WO 88/08854, Published 11/17/1988) as evidenced by the specification in view of Oosterwijk et al (b) (Seminars in Oncology. 1995. 22(1): 34-41) in view of Robinson et al (U.S. Patent 5,618,920; Issued 4/8/1997) and in view of Queen et al (U.S. Patent 5,530,101; Issued 6/25/1996), is maintained. These references are cited in PTO-892 mailed on 06/20/2006.

At page 2 of the response filed August 4, 2008, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that "the G250 antibody was protected by confidentiality and restricted use agreements between Leiden University (Dr. Gorter), Centocor, Dr. Daniel den Hoed Hospital in Rotterdam (Dr. Bolhuis), and Ludwig Institute for Cancer Research (Dr. Ritter). The agreements were transferred from Centocor to Wilex on February 22, 1999. The Declarations submitted in this Response and in previous responses attest to the fact that Dr. Sven Warnaar set bars for the distribution and usage of the G250 antibody prior to allocating the G250 antibody. Clearly, the G250 antibody was not available for public use and was protected by confidentiality and restricted use agreements. There is no evidence of any public deposition or sale of the G250 hybridoma cells". (see page 4 of the response).

In response, the above arguments have been carefully and fully considered but are not persuasive. The prior art indicates that the G250 antibody was also in the possession of e.g., Lindholm (WO 200102431 A1, January 2001), Choudhary et al (Int. J. Can, 82:1562-1568, 1999), Danen (Exp Cell Res., 238:188-196, 1998), Lal et al (JNCI 93(17):1337-1343, 2001), Tso et al (Can Res., 61:7925-7933, 2001) and Shinkai (Jpn. J. Can Res, 92:1138-1145, 2001). Notably, as set forth in below 35 USC 102(b) rejection, Lindholm teaches the heavy and light chain sequences of a G250 antibody which comprises the instantly recited amino acid sequences. Furthermore, Choudhary et al discloses that instead of Dr. Sven Warnaar providing the antibody, that Dr. Bolhuis provided the G250 antibody (see page 563, left column), while Danen et al discloses that Dr. Oosterwijk provided the G250 antibody (see page 189, left column). Notably, none of the above references set forth that the G250 antibody was provided by Dr. Warnaar, nor disclose any restrictions placed on the use of the antibody.

For these reasons and the reasons set forth previously, and after careful and full consideration of Applicant's response, Applicant contention that the rejection should be withdrawn is not persuasive because the Examiner maintains that the claimed invention as a whole was obvious to one of ordinary skill in the art in view of these references. Therefore, this rejection of claims 1-11 is maintained.

15. The rejection of claims 1-11 under 35 U.S.C. 103(a) as being unpatentable over Weijtens et al (The Journal of Immunology, 157:836-843, 1996) as evidenced by the specification in view of Oosterwijk et al (b) (Seminars in Oncology. 1995. 22(1): 34-41) in view of Orlandi et al (Proc. Natl. Acad. Sci. USA, 86:3833-3837, 1989) in view of Cabilly et al (U.S Patent 4816567, Issued 3/89) in view of Robinson et al (U.S. Patent 5618920, Filed 4/94) in view of Huston et al (U.S. Patent 5258498, Issued 11/93) and in view of Queen et al (U.S. Patent 5,530,101; Issued 6/25/1996), is maintained. These references are cited partly in PTO-892 mailed on 06/20/2006 and partly in PTO-892 mailed on 02/26/2007.

At page 2 of the response filed August 4, 2008, Applicant has traversed this ground of rejection on the same basis as set forth in the above 35 USC 103 rejection.

Applicant's arguments have been carefully considered but not found persuasive for the reasons set in the response to Applicant's arguments in the above 35 USC 103 rejection.

For these reasons and the reasons set forth previously, and after careful and full consideration of Applicant's response, Applicant contention that the rejection should be withdrawn is not persuasive because the Examiner maintains that the claimed invention as a whole was obvious to one of ordinary skill in the art in view of these references. Therefore, this rejection of claims 1-11 is maintained.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is

> claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention*.

In the instant case, the claims are directed to a structurally and functionally diverse genus of recombinant vector systems comprising at least one copy of a first nucleic acid encoding the antigen-binding site of the heavy chain of an antibody, said first nucleic acid comprising a nucleotide sequence encoding SEQ ID NO:24, a nucleotide sequence encoding SEQ ID NO:25, and a nucleotide sequence encoding SEQ ID NO:26, and at least one copy of a second nucleic acid encoding the antigen-binding site of the light chain of an antibody, said second nucleic acid comprising a nucleotide sequence encoding SEQ ID NO:27, a nucleotide sequence encoding SEQ ID NO:28, and a nucleotide sequence encoding SEQ ID NO:29 (see claim 1) or to a diverse genus of methods for the recombinant production of structurally and functionally diverse polypeptides having an antigen-binding site comprising (a) providing a recombinant vector system according to claim 1, (b) introducing the recombinant vector system into a suitable host cell, (c) culturing the host cell under suitable conditions in a medium whereby an expression of the polypeptide takes place and (d) obtaining the expressed product from the medium and/or the host cell (see claim 4).

As a first point to address the reasons why the specification has not adequately described recombinant vector systems encoding antigen-binding sites, or the methods of producing polypeptides encoding antigen-binding sites, it is noted that while the specification has described recombinant vector systems encoding an antibody or

antigen-binding fragment thereof, wherein said antibody or antigen-binding fragment thereof specifically binds the G250 antigen and wherein said antibody or antigen-binding fragment thereof comprises a nucleic acid encoding the heavy chain variable domain of an antibody which comprises a nucleotide sequence encoding SEQ ID NO:24, a nucleotide sequence encoding SEQ ID NO:25, and a nucleotide sequence encoding the amino acid sequence HRSGYFSMDY, and a nucleic acid encoding the light chain variable domain of an antibody which comprises a nucleotide sequence encoding SEQ ID NO:27, a nucleotide sequence encoding SEQ ID NO:28, and a nucleotide sequence encoding SEQ ID NO:29, as well as describing methods of producing said antibodies or antigen-binding fragments thereof (see e.g., Figure 1, page 1 and page 10 of the specification), the claimed recombinant vector systems need not encode or produce such an antibody or antigen binding fragment thereof, and therefore the claims do not require the claimed genus of recombinant vector systems to encode the particularly identifying structural feature of this antibody.

Notably, as a first point, the claims do not require that the recited "recombinant vector systems" encode an antibody which binds any particular well-described antigen or encode an antigen-binding fragment thereof which binds any particular well-described antigen and therefore there can be no correlation of any particular identifying structural feature with any function of the claimed antibodies. For example, claims 1 and 4 do not recite that recombinant vector system encodes an antibody and none of the claims recite binding to any antigen. Thus, while the claims broadly encompass a diverse genus of "recombinant vector systems" encoding a polypeptide having some antigen-binding site, which might not bind any antigen at all or which might bind antigens other than the disclosed G250 antigen, the specification fails to adequately describe these "recombinant vector systems", as a whole, because the skilled artisan could not immediately envision, recognize or distinguish as least most of its members from other "recombinant vector systems", as the specification fails to describe its members as sharing any particularly identifying (i.e., substantial) structural feature, which correlates with any one particularly identifying functional feature that is also shared by many, if not all, of those "recombinant vector systems".

Accordingly, it is submitted that the specification fails to provide a representative description of at least a substantial number of the recombinant vector systems that are encompassed by the recited genus. Absent such a clear and particular description of the whole of the recombinant vector systems that are encompassed by the recited genus, it appears that the specification would not adequately describe the claimed recombinant vector systems in a manner that would reasonably convey to the skilled artisan that Applicant had possession of that subject matter at the time the application was filed.

To elaborate on why the claimed antibodies and functional fragments lack adequate written description, Mariuzza et al. (*Annu. Rev. Biophys. Biophys. Chem.* 1987; **16**: 139-159) reviews the structural basis of antigen-antibody recognition and teaches that a naturally occurring antibody comprises two polypeptides, the so-called light and heavy chains. The antigen-combining site of an antibody is a three-dimensional structure, which fully comprises six "complementarity-determining regions" (CDRs), three each from the light and heavy chains. The amino acid sequences of the CDRs are hypervariable, as the amino acid residues contained within the CDRs determine much of antibody's antigen-binding specificity. Of the amino acid residues of the antibody contacting the antigen, six are within the light chain, nine are within the heavy chain, and two are within the constant or nearly constant "framework" regions.

In view of Mariuzza et al., it is apparent that antibodies having less than all six CDRs that form the antigen binding site of an antibody in their proper context of heavy and light chain variable domains does not suffice to describe the particularly identifying structural feature of the antibody that correlates with the antibody's ability to bind to the antigen. Absent a description of the at least minimal structural features correlating with a functional ability to bind to a particular antigen, which are shared by members of a genus commonly sharing this function, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish members of the genus from other antibodies. For this reason, the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

While the prior art teaches well-known and conventional methodology for producing "humanized" monoclonal antibodies by CDR grafting heavy and light chain CDRs into corresponding human heavy and light chain frameworks to give an antibody that binds the same epitope on an antigen as the parent antibody with generally similar functions, one of skill in the art would not immediately envision or recognize chimeric or humanized monoclonal antibodies comprising less than all 6 CDRs of a parent antibody in the proper context of heavy and light chain frameworks as retaining the binding affinity, specificity and function of the parent antibody.

For example, Gussow et al. (Methods in Enzymology. 1991; 203: 99-121) teach the general methodology for making humanized antibodies; see entire document. One means for producing a humanized antibody involves grafting the six CDRs from the light and heavy chain variable regions from a murine antibody into the framework of a human antibody. However, in general, if only one or two of the CDRs from either the light or heavy chain variable region were to be grafted, but not all three, the resultant antibody would not be expected to retain the binding affinity and specificity of the parent antibody. Therefore, since it is expected that all 6 CDRs need to be grafted into antibody framework regions to retain the requisite affinity and specificity of the parent antibody, antibodies that do not comprise all 6 CDRs grafted into framework regions, would not be immediately envisioned or recognized by one of skill in the art as having similar functions as the parent antibody.

Furthermore, while the prior art teaches some understanding of the structural basis of antigen-antibody recognition and conventional methodology for humanizing monoclonal antibodies, it is aptly noted that the art is characterized by a high level of unpredictability, since the skilled artisan still cannot accurately and reliably predict the consequences of amino acid substitutions, insertions, and deletions in the antigen-binding domains and surrounding framework regions of antibodies. For example, Giusti et al. (*Proc. Natl. Acad. Sci. USA.* 1987 May; **84** (9): 2926-2930) teaches the specificity and affinity of an antibody is exquisitely sensitive to amino acid substitutions within the primary structure of the antibody, since only a single amino acid substitution in the heavy chain of an antibody completely altered the binding specificity of an antibody that

binds phosphocholine, such that the altered antibody fails to bind phosphocholine but instead binds DNA; see entire document (e.g., the abstract). This unpredictability of single amino acid changes in an antibody is underscored by Winkler et al (J. Imm., 265:4505-4514, 2000) who teach that single amino acid changes in antibody side chains can result in unpredictable and substantial changes in antibody specificity; see entire document (e.g., the abstract). Chien et al. (*Proc. Natl. Acad. Sci. USA.* 1989 Jul; **86** (14): 5532-5536) teaches that significant structural and functional changes in an antigen-binding site can be caused by amino acid substitutions in the primary structure of an antibody, including substitutions at a site remote from the complementarity determining regions of the antigen-binding domain; see entire document (e.g., the abstract). Similarly, but more recently, Caldas et al. (*Mol. Immunol.* 2003 May; **39** (15): 941-952) teaches an unexpected effect of substituting a framework residue upon binding specificity during the humanization of an antibody that binds CD18; see entire document (e.g., the abstract).

The Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568).

Additionally, "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

"Guidelines" states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims are directed to a genus of structurally disparate antibodies, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

In summary, the specification fails to describe at least a substantial number of the claimed recombinant vector systems and furthermore fails to describe a representative number of the recombinant vector systems encompassed by the claims. Moreover, the specification does not describe a correlation between any particularly identifying (i.e., substantial) structural feature that describes the presupposed representative species, which is shared by at least most of the other members of the genus, and any one particularly identifying functional feature also shared by at least most that may be attributed to the presence of the particularly identifying structural feature. Consequently, the skilled artisan could not immediately envision, recognize or distinguish at least a substantial number of the members of the claimed genus of recombinant vector systems and therefore the supporting disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

In conclusion, given the lack of particularity with which the claimed recombinant vector systems are described in the specification, it is submitted that the skilled artisan would not recognize that Applicant was in possession of recombinant vector systems that were reasonably representative of the claimed recombinant vector systems. Therefore, the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

18. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a NEW MATTER rejection.

In this case, in the amendment filed December 20, 2008, claim 1 has been amended to from reciting that the nucleic acid encodes the CDR3 region designated H3 to "a nucleotide sequence encoding SEQ ID NO:26" i.e., SGYFSMDY.

Applicant has indicated that representative support for this amendment can be found in Figure 1.

However, as originally filed, Figure 1 identifies H3 with the amino acid sequence HRSGYFSMDY (see Figure 1).

Accordingly, it is submitted that amending the claims to recite "a nucleotide sequence encoding SEQ ID NO:26" does not have written support in the specification as filed, because it is not apparent that the amino acid sequence of SEQ ID NO:26 was originally contemplated as CDR3 of the heavy chain.

Therefore, given the apparent difference in the breadth of the claims and that of the pertinent disclosures it is submitted that this clearly illustrates that such amendments have in fact introduced new concepts, thereby violating the written description requirement set forth under 35 U.S.C. §112, first paragraph.

Otherwise this issue might be resolved if Applicant were to point to other disclosures in the specification, including the claims, as originally filed, which are believed to provide the necessary written support for the language of the instant claims.

19. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** recombinant vector systems encoding an antibody or antigen-binding fragment thereof, wherein said antibody or antigen-binding fragment thereof specifically binds the G250 antigen and wherein said antibody or antigen-binding fragment thereof comprises a nucleic acid encoding the heavy chain variable domain of an antibody which comprises a nucleotide sequence encoding SEQ ID NO:24, a nucleotide sequence encoding SEQ ID NO:25, and a nucleotide sequence encoding the amino acid sequence HRSGYFSMDY[1], and a nucleic acid encoding the light chain variable domain of an antibody which comprises a nucleotide sequence encoding SEQ ID NO:27, a nucleotide sequence encoding SEQ ID NO:28, and a nucleotide sequence encoding SEQ ID NO:29, as well as **being enabling for using** methods of producing said antibodies or antigen-binding fragments thereof, **does not reasonably provide enablement for making and using** the full scope of the recited "recombinant expression vectors" and methods .

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue".

[1] It is noted that in order to comply with the sequence rules, such a sequence would need to be identified by SEQ ID NO:.

These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

In this case, the claims are broadly directed to a diverse genus of recombinant vector systems comprising at least one copy of a first nucleic acid encoding the antigen-binding site of the heavy chain of an antibody, said first nucleic acid comprising a nucleotide sequence encoding SEQ ID NO:24, a nucleotide sequence encoding SEQ ID NO:25, and a nucleotide sequence encoding SEQ ID NO:26, and at least one copy of a second nucleic acid encoding the antigen-binding site of the light chain of an antibody, said second nucleic acid comprising a nucleotide sequence encoding SEQ ID NO:27, a nucleotide sequence encoding SEQ ID NO:28, and a nucleotide sequence encoding SEQ ID NO:29 (see claim 1) or to a diverse genus of methods for the recombinant production of structurally and functionally diverse polypeptides having an antigen-binding site comprising (a) providing a recombinant vector system according to claim 1, (b) introducing the recombinant vector system into a suitable host cell, (c) culturing the host cell under suitable conditions in a medium whereby an expression of the polypeptide takes place and (d) obtaining the expressed product from the medium and/or the host cell (see claim 4).

As a first point, since the claims are not limited to recombinant vector systems encoding antibodies or antigen-binding fragments thereof that specifically bind to one well-characterized antigen, but entirely lack antigen-binding function, one of skill in the

art would be subject to undue and unreasonable experimentation to make and use the claimed products and methods reasonably commensurate in scope with the claims. For example, one of skill in the art would be subject to undue experimentation to make recombinant vector systems comprising the claimed structural features wherein the antibody binds to an antigen other than the disclosed G250 antigen. In this case, the specification provides no specific, non-general guidance as to how recombinant vector systems might be altered to change the antigen-binding specificity of a polypeptide produced by said vector system for any other antigen, and as will be explained in further detail below, amino acid alterations in an antibody made relative to a parent antibody have highly unpredictable effects on antigen-binding specificity. For these reasons, one of skill in the art would be subject to undue experimentation to make antibodies commensurate to the full scope of the claimed invention.

As noted by Mariuzza et al. (*supra*), it is well established fact in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable domains of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc. Natl. Acad. Sci. USA 1982 Vol. 79: page 1979). Rudikoff et al teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that recombinant vector systems encoding polypeptides that do not contain all of the 6 CDRs of the parent antibody in

their proper context of heavy and light chain variable domains, respectively, would retain the binding function of the parent antibody. For example, as set forth in the above rejection of the claims as lacking adequate written description, Gussow et al (*supra*) teaches conventional methodologies for "humanizing" monoclonal antibodies which generally involve grafting the six CDRs from the light and heavy chain variable regions from a murine antibody into the framework of a human antibody. However, in general, if only one or two of the CDRs from the light and heavy chain variable region were to be grafted, but not all three, the resultant antibody would not be expected to retain the binding affinity and specificity of the parent antibody.

Thus, while the prior art teaches some understanding of the structural basis of antigen-antibody recognition and conventional methodology for humanizing monoclonal antibodies, it is aptly noted that the art is characterized by a high level of unpredictability, since the skilled artisan still cannot accurately and reliably predict the consequences of amino acid substitutions, insertions, and deletions in the antigen-binding domains and surrounding framework regions of antibodies. For example, Giusti et al. (*supra*) teaches the specificity and affinity of an antibody is exquisitely sensitive to amino acid substitutions within the primary structure of the antibody, since only a single amino acid substitution in the heavy chain of an antibody completely altered the binding specificity of an antibody that binds phosphocholine, such that the altered antibody fails to bind phosphocholine but instead binds DNA; see entire document (e.g., the abstract). Chien et al. (*supra*) teaches that significant structural and functional changes in an antigen-binding site can be caused by amino acid substitutions in the primary structure of an antibody, including substitutions as a site remote from the complementarity determining regions of the antigen-binding domain; see entire document (e.g., the abstract). Similarly, but more recently, Caldas et al. (*supra*) teaches an unexpected effect of substituting a framework residue upon binding specificity during the humanization of an antibody that binds CD18; see entire document (e.g., the abstract).

The art of engineering functional recombinant antibodies, such as those to which the claims are directed, is even more confounded by findings that residues, which are

positioned outside the recognized boundaries of the canonical CDRs, may contribute substantially to the interaction of an antibody and an antigen. For example, MacCallum et al. (*J. Mol. Biol.* 1996 Oct 11; **262** (5): 732-745) describes the discovery that although the residues of CDR3 of the heavy and light chains are dominant determinants of the interaction, a number of essential residues contacting the antigen have been placed outside the regions that are recognized using the conventional or standard definitions of the CDRs, which are generally used to define the components of the antigen binding site of the antibody; see entire document (e.g., page 733, column 2). Moreover, MacCallum et al. teaches an appreciation of the fact that residues within the CDRs that do not actually make contact with the antigen may be important because of their contributions to the conformation of the antibody's antigen recognition site; see, e.g., page 735, column 1.

Making further apparent the unpredictability of the importance of residues within the CDRs and other parts of an antibody, which must instead be determined empirically, Holm et al. (*Mol. Immunol.* 2007 Feb; **44** (6): 1075-1084) describes the mapping of residues important to the interaction of an anti-cytokeratin antibody with the antigen, where although residues in the CDR3 of the heavy chain were determined to be essential, they disclose their *unexpected* finding that a residue in CDR2 of the light chain forms a necessary part of the antigen binding site of the antibody contacting the antigen; see entire document (e.g., the abstract). Thus, as recently as 2007, there are reports indicating despite the progress made toward understanding the interactions of antibodies and antigens, because of the unpredictable nature of the art, much information concerning the specificity and/or affinity of any given antibody cannot be gleaned by routine and conventional experimentation, but instead must be gathered by rigorous and undue experimentation. For these reasons, one of skill in the art would be subject to undue and unreasonable experimentation to make and use recombinant vector systems encoding polypeptides commensurate in scope with the claimed recombinant vector systems which could bind to any antigen.

Furthermore, while the specification teaches one of skill in the art how to use recombinant vector systems encoding an antibody or antigen-binding fragment thereof,

wherein said antibody or antigen-binding fragment thereof specifically binds the G250 antigen and wherein said antibody or antigen-binding fragment thereof comprises a nucleic acid encoding the heavy chain variable domain of an antibody which comprises a nucleotide sequence encoding SEQ ID NO:24, a nucleotide sequence encoding SEQ ID NO:25, and a nucleotide sequence encoding the amino acid sequence HRSGYFSMDY, and a nucleic acid encoding the light chain variable domain of an antibody which comprises a nucleotide sequence encoding SEQ ID NO:27, a nucleotide sequence encoding SEQ ID NO:28, and a nucleotide sequence encoding SEQ ID NO:29, since the claims are not drawn to antibodies or antigen-binding fragments thereof that bind any particular antigen, one of skill in the art would be subject to undue experimentation to identify a use for polypeptides broadly encompassed by the claims which do not bind the disclosed G250 antigen.

Applicant is reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

In conclusion, upon careful and full consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enabled the skilled artisan to make and use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

21. Claims 1-7 and 9-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Lindholm (WO 200102431 A1, January 2001) as evidenced by US Patent 5969108 (McCafferty et al, 1999).

Claims 1-3 are herein drawn to a recombinant vector system comprising at least one copy of a first nucleic acid encoding the antigen-binding site of the heavy chain of an antibody, said first nucleic acid comprising a nucleotide sequence encoding SEQ ID NO:24, a nucleotide sequence encoding SEQ ID NO:25, and a nucleotide sequence encoding SEQ ID NO:26, and at least one copy of a second nucleic acid encoding the antigen-binding site of the light chain of an antibody, said second nucleic acid comprising a nucleotide sequence encoding SEQ ID NO:27, a nucleotide sequence encoding SEQ ID NO:28, and a nucleotide sequence encoding SEQ ID NO:29, wherein the first and second nucleic acids encoding the antigen-binding site of the heavy chain and of the light chain have separate expression control sequences which can be on the same or different vectors. Claims 4-7 and 9-10 are herein drawn to methods of producing a product comprising a polypeptide, such as an antibody or antibody fragment, by (a) providing a recombinant vector system according to claim 1, (b) introducing the recombinant vector system into a suitable host cell, (c) culturing the host cell under suitable conditions in a medium whereby an expression of the polypeptide takes place and (d) obtaining the expressed product from the medium and/or the host cell. Dependent claims further recite that the host cell in mammalian a modification of the vector system or that the method further comprises coupling a cytotoxic agent to the product. Notably, since the modification only recites that the amino acid sequence is

not altered, the claims are broadly, but reasonably interpreted to include process steps purifying the vector or dissolving the vector in an appropriate buffer because such steps inherently modify the vector system without changing the amino acid sequence and would occur after a vector system has been provided.

Lindholm teaches recombinant vector systems comprising nucleic acids which encode the variable heavy chain domain and the variable light chain domain of the G250 antibody and teach the amino acid sequences of these domains as SEQ ID NO:15 and SEQ ID NO:16 and methods of producing products comprising such variable heavy chain domain and the variable light chain domain antibodies or antibody fragments, such as Fab fragments which inherently have separate expression control sequences (see entire document, e.g., SEQ ID NO:15 and 16, and pages 6-8). Notably, these sequences comprise the amino acid sequences set forth in the instantly claimed SEQ ID NOs[2]. Furthermore, Lindholm teaches that the expression of such products in mammalian COS cells and that the expressed product can be conjugated to cytotoxic agents such as an adenovirus.

Finally, while Lindholm does not expressly teach that that Fabs may be expressed from the same or different recombinant vector, one of skill in the art would immediately recognize that Lindholm's disclosure of Fab fragments encompasses expression from either the same or different vectors as Fab expression systems were known in the art to use either. For example, as evidenced by McCafferty et al “heavy and light chains encoded on the same vector(construct II), or on different vectors (constructs III and IV) can be displayed as Fab fragments” (see e.g., columns 68 and 69).

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[2] The instantly recited amino acid sequences have been underlined in the variable heavy chain domain and variable light chain domain disclosed by Lindholm, respectively for reference : SEQ ID No:15:
SLKLSCAASGFTFSNYYMSWVRQTPEKRLELVAAINSDGGITYYLDTVKGRFTISRDNAKNTLYLQMSSLK
SEDTALFYCARHRSGYFSMDYWGQGTSVTVSSGS
SEQ ID No:16:
DIVMTQSQRFMSTTVGDRVSITCKASQNVVSAVAWYQQKPGQSPKLLIYSASNRYTGVPDRFTGSGSGT
DFTLTISNMQSEDLADFFCQQYSNYPWTFGGGTKLEIKRADAAPTVS

Thus, the recombinant vector systems of Lindholm appear structurally and materially indistinguishable from the instantly recited recombinant vector systems and the methods of Lindholm appear manipulatively and materially indistinguishable from the instantly recited methods. Therefore, absent a showing of any difference, the claimed products and methods and the products and methods disclosed by the prior art are deemed the same and Lindholm anticipates the claimed invention.

22. Claims 1-2 and 4-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Steffens et al (JCO, 15(4):1529-1537, 1997, cited by Examiner 6/20/06) as evidenced by Velders et al (Can. Res., 54:1753-1759, 1994, IDS field 8/29/08).

Claims 1-2 are herein drawn to a recombinant vector system comprising at least one copy of a first nucleic acid encoding the antigen-binding site of the heavy chain of an antibody, said first nucleic acid comprising a nucleotide sequence encoding SEQ ID NO:24, a nucleotide sequence encoding SEQ ID NO:25, and a nucleotide sequence encoding SEQ ID NO:26, and at least one copy of a second nucleic acid encoding the antigen-binding site of the light chain of an antibody, said second nucleic acid comprising a nucleotide sequence encoding SEQ ID NO:27, a nucleotide sequence encoding SEQ ID NO:28, and a nucleotide sequence encoding SEQ ID NO:29, wherein the first and second nucleic acids encoding the antigen-binding site of the heavy chain and of the light chain have separate expression control sequences which can be on different vectors. Claims 4-11 are herein drawn to methods of producing a product comprising a polypeptide, such as an antibody or antibody fragment, by (a) providing a recombinant vector system according to claim 1, (b) introducing the recombinant vector system into a suitable host cell, (c) culturing the host cell under suitable conditions in a medium whereby an expression of the polypeptide takes place and (d) obtaining the expressed product from the medium and/or the host cell. Dependent claims further recite that the host cell is mammalian, that a modification of the vector system occurs between steps (a) and (b), or that the method further comprises coupling a cytotoxic agent or diagnostic agent, such as a radioisotope to the product. Notably, since the

modification only recites that the amino acid sequence is not altered, the claims are broadly, but reasonably interpreted to include process steps purifying the vector or dissolving the vector in an appropriate buffer because such steps inherently modify the vector system without changing the amino acid sequence and would occur after a vector system has been provided.

Steffens et al teach recombinant vector systems comprising nucleic acids which encode a recombinant chimeric G250 antibody (see entire document, e.g., page 1530, left column). While, Steffens et al do not expressly teach the amino acid sequences of the G250 antibody, the amino acid sequence of the chimeric antibody is an inherent property. Notably, the Office lacks the resources and facilities to sequence the antibody disclosed by the prior art and compare it to the claimed antibody sequences to establish whether there are any differences. Consequently, in the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed antibody sequences are different from the sequences inherently present in the antibody taught by the prior art. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA, 1977); and *Ex parte Gray*, 10 USPQ2d 1922 1923 (PTO Board of Patent Appeals and Interferences, 1988 and 1989).

Furthermore, Steffens et al teaches that that the recombinant chimeric G250 antibody was produced by methods described in Velders et al. Notably, as evidenced by Velders et al, separate heavy and light chain expression vectors were introduced into murine myeloma cells from which the antibody was then obtained (see entire document, e.g., page 1754, right column).

Finally, Steffens et al teach labeling the chimeric G250 antibody with radioactive iodine markers, which because it is radioactive, is also a cytotoxic agent (see entire document, e.g., page 1530).

Thus, the recombinant vector systems of Steffens et al appear structurally and materially indistinguishable from the instantly recited recombinant vector systems and the methods of Steffens et al appear manipulatively and materially indistinguishable from the instantly recited methods. Therefore, absent a showing of any difference, the

claimed products and methods and the products and methods disclosed by the prior art are deemed the same and Steffens et al anticipates the claimed invention.

Claim Rejections - 35 USC § 103

23. Claims 4, 7, 8 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lindholm (WO 200102431 A1, January 2001) in view of Steffens et al (JCO, 15(4):1529-1537, 1997).

Claims 4, 7, 8 and 11 are herein drawn to the method of claim 4, further comprising conjugating a radioactive marker to the expressed product.

As set forth in the above 102(b) rejection, Lindholm teaches methods of making recombinant G250 antibodies and antibody fragments, such as a Fab fragment, which comprise the instantly recited SEQ ID Nos and conjugating such products to another agent.

However, Lindholm does not expressly teach that such agents can be a radioactive marker.

This deficiency is made up for in the teachings of Steffens et al.

Steffens et al coupling G250 antibodies with radioactive iodine markers to study specificity of binding of the antibodies in competitive binding assays (see entire document, e.g., page 1530, left column).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to couple the G250 products of Lindholm with the radioactive iodine markers of Steffens et al, because one of ordinary skill in the art would have been motivated to assay the specificity of binding of the Lindholm constructs in competitive binding assays. Furthermore, one of ordinary skill in the art would have a reasonable expectation of success at the time the invention was made to make such a product by these methods because Steffens et al teach that processes to radiolabel antibody products were known in the art.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

24. Claims 1 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Steffens et al (JCO, 15(4):1529-1537, 1997) as evidenced by Velders et al (Can. Res., 54:1753-1759, 1994), in view of US Patent 6057098 (Buechler et al, 2000).

Claims 1 and 3 are herein drawn to a recombinant vector system comprising at least one copy of a first nucleic acid encoding the antigen-binding site of the heavy chain of an antibody, said first nucleic acid comprising a nucleotide sequence encoding SEQ ID NO:24, a nucleotide sequence encoding SEQ ID NO:25, and a nucleotide sequence encoding SEQ ID NO:26, and at least one copy of a second nucleic acid encoding the antigen-binding site of the light chain of an antibody, said second nucleic acid comprising a nucleotide sequence encoding SEQ ID NO:27, a nucleotide sequence encoding SEQ ID NO:28, and a nucleotide sequence encoding SEQ ID NO:29, wherein the first and second nucleic acids encoding the antigen-binding site of the heavy chain and of the light chain have separate expression control sequences which are on the same vector.

Steffens et al teach what is set forth in the above 102(b) rejection.

Notably, while Steffens et al teach recombinant vector systems which use different vectors for the heavy and light chain constructs, Steffens et al does not expressly teach that these constructs can be on the same vector.

This deficiency is made up for in the teachings of Buechler et al. Buechler et al teach that it is known in the art that heavy and light chain constructs can either be cloned into different vectors or the same vector for recombinant antibody production (see entire document, e.g., column 10).

Thus, in view of these references, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made because recombinant vector systems used to express antibody products from the same vector were known and predictable in the art. Accordingly, one of ordinary skill in the art would not have found it inventive to predictably substitute a recombinant vector system that is on the same vector for the vector system of Steffens et al which is on different vectors, because they would have immediately envisioned that either system would be predictably effective in expressing the recombinant antibody.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

25. No claims are allowed.

26. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

/bd/
Examiner, Art Unit 1643
December 16, 2008